BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/087066 A1

(51) International Patent Classification[7]: C07D 241/04, C07C 259/06

(21) International Application Number: PCT/KR03/00721

(22) International Filing Date: 10 April 2003 (10.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2002-0019712 11 April 2002 (11.04.2002) KR

(71) Applicants *(for all designated States except US)*: **SK CHEMICALS, CO., LTD.** [KR/KR]; 600 Jungja 1-dong, Jangan-ku, Suwon-shi, Kyungki-do 440-301 (KR). **IN2GEN CO., LTD.** [KR/KR]; 6th Floor, Cancer Research Institute, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-799 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KIM, Dae-Kee** [KR/KR]; 4-705 Shindonga Apt., Bong-dong 481, Dongjak-ku, Seoul 156-768 (KR). **LEE, Ju Young** [KR/KR]; 105-1502 Dongshin Apt., 401 Jungja-dong,, Jangan-ku, Suwon-shi, Kyungki-do 440-300 (KR). **LEE, Nam Kyu** [KR/KR]; 123-108 Joogong Apt., 333 Chunchun-dong, Jangan-ku, Suwon-shi, Kyungki-do 440-330 (KR). **KIM, Jae-Sun** [KR/KR]; 1146-3 15/5 Seryu 2-dong, Kwonsun-ku, Suwon-shi, Kyungki-do 441-112 (KR). **LEE, Junwon** [KR/KR]; 638-1404 Sejong Apt., Kwangjeong-dong, Gunpo-Shi, Kyungki-do 435-705 (KR). **LEE, Suk Ho** [KR/KR]; 1204-1504 Joogong Apt., 449-6 Chulsan 3-dong, kwangmyung-shi, Kyungki-do 423-033 (KR). **CHOI, Jin Young** [KR/KR]; 127-108 Chunchun-Joogong Apt., Chunchun-dong, Jangan-ku, Suwon-shi, Kyungki-do 440-330 (KR). **RYU, Je Ho** [KR/KR]; 401 Samyang-villa, 654-6 Daerim 3-dong, Youngdeungpo-ku, Seoul 150-073 (KR). **KIM, Nam Ho** [KR/KR]; 101 1409 Hyundai Apt., Eunghang-dong, Joongwon-ku, Sungnam-shi, Kyungki-do 462-150 (KR). **IM, Guang-Jin** [KR/KR]; 406-1202 Hyundai Apt., 1343 Sa-dong, Ansan-shi, Kyungki-do 425-170 (KR). **KIM, Tae Kon** [KR/KR]; SK Chemicals Institute, Jungja-dong, Jangan-ku, Suwon-shi, Kyungki-do 440-300 (KR). **SEO, Jung-Woo** [KR/KR]; 139-602 Gwanak Dream Town, Bongchun 5-dong, Gwanak-ku, Seoul 151-055 (KR). **BANG, Young-Jue** [KR/KR]; 120-694 Hyundai Apt., 434 Apgujeong-dong, Kangnam-ku, Seoul 135-110 (KR).

(74) Agent: **HUH, Sang-Hoon**; 16th Fl., Woori Investment Bank Bldg., 826-20, Yeoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/087066 A1

(54) Title: α,β-UNSATURATED HYDROXAMIC ACID DERIVATIVES AND THEIR USE AS HISTONE DEACETYLASE INHIBITORS

(57) Abstract: Disclosed are agents that inhibit histone deacetylase. More specifically, the present invention relates to novel hydroxamic acid derivatives or pharmaceutically acceptable salts thereof for anticancer agents or other therapeutic agents based on their histone deacetylase inhibitory activity.

α,β-UNSATURATED HYDROXAMIC ACID DERIVATIVES AND THEIR USE AS HISTONE DEACETYLASE INHIBITORS

BACKGROUND OF THE INVENTION

Field of the invention

This invention relates to histone deacetylase inhibiting agents. In particular, the present invention relates to novel hydroxamic acid derivatives or pharmaceutically acceptable salts thereof for anticancer agents or other therapeutic agents based on their histone deacetylase inhibitory activity.

Description of the art

Cancer is one of the most common cause of death in the developed world. Despite advances in the diagnosis and management of many cancers, only minor improvements in cure and survival rates have been realized. The incidence of cancer is rising as a result of ageing populations and complex environmental and lifestyle factors. Cancer imposes great costs on society and individuals via premature disability, mortality and high treatment costs. To date many anticancer drugs have been investigated, but no satisfactory drugs have been discovered. So an anticancer drug with reduced toxicity and high therapeutic effect has been desired.

Key nuclear processes such as DNA replication, transcription, repair, and rearrangements during differentiation are influenced by chromatin structure and the binding of regulatory proteins to DNA. These processes can be modulated by the acetylation level of nucleosomal histones. Histone deacetylases and the family of histone acetyltransferases are involved in determining this acetylation of histones, which play a role in regulation of gene expression. Increasing evidence indicates that cellular proteins involved in the regulation of proliferation and differentiation exert their

function by recruitment of histone acetyltransferases or deacetylases. In various cases aberrant histone acetylation has been linked to malignant disease.

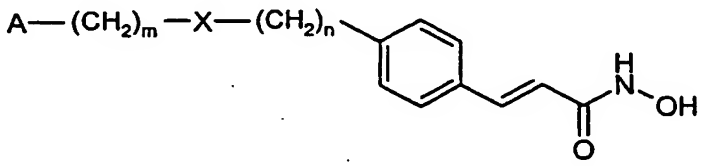
A number of histone deacetylase inhibitors have been identified that induce cultured tumor cells to undergo growth arrest, differentiation, and/or apoptotic cell death. Several of these agents, the hydroxamic acid based histone deacetylase inhibitors in particular, inhibit tumor growth in animals at doses that cause little or no toxicity [Paul A. Marks et al., Current Opinion in Oncology, 2001, 13, 477-483].

SUMMARY OF THE INVENTION

An objective of this invention is to provide a compound which has a histone deacetylase inhibitory activity and is useful as a therapeutic or improving agent for malignant tumors.

We have attempted to achieve the above objective and have found that novel α,β-unsaturated hydroxamic acid derivatives having histone deacetylase inhibitory activity show promising antitumor effect.

This invention provides compounds represented by formula (1) or pharmaceutically acceptable salts thereof



1

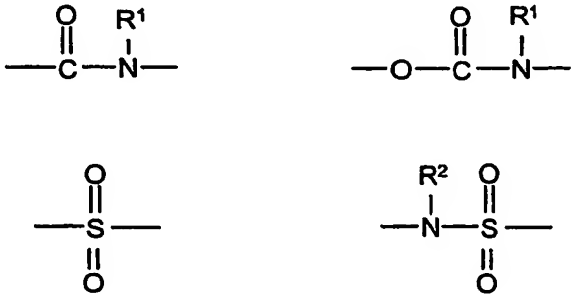
wherein A is an optionally substituted phenyl or aromatic heterocyclic group which has 1 to 4 substituents selected from the group consisiting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group

having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkoxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group, an aromatic heterocyclic group and a heterocyclic group, said heterocyclic group being optionally substituted with an alkyl group having 1 to 4 carbons, a benzyl group, or a pyridylmethyl group;

m is an integer of 0 to 4;

n is an integer of 1 to 4;

X is a moiety having a structure selected from those illustrated in formula (2)



2

R^1 and R^2 are independently H or an optionally substituted alkyl group having 1 to 4 carbons

DETAILED DESCRIPTION OF THE INVENTION

Throughout this specification, the term aromatic heterocyclic group means a 5–6 membered aromatic ring containing one or more atoms selected from oxygen, sulfur and nitrogen atoms on the ring, said ring being optionally condensed with a carbon ring or other heterocyclic ring.

Examples include pyrrole, indole, carbazole, imidazole, pyrazole, benzimidazole, pyridine, naphthyridine, furopyridine, thienopyridine, pyrrolopyridine, oxazolopyridine, imidazolopyridine, thiazolopyridine, quinoline, isoquinoline, acridine, phenanthridine, pyridazine, pyrimidine, pyrazine, cinnoline, phthaladine, quinazoline, naphthylidine, quinoxaline, isoxazole, benzisoxazole, oxazole, benzoxazole, benzoxadiazole, isothiazole, benzisothiazole, thiazole, benzthiazole, benzthiadiazole, furan, benzofuran, thiophen, benzothiophen, and the like.

The term heterocyclic group means a 5–6 membered ring containing one or more atoms selected from oxygen, sulfur and nitrogen atoms on the ring, said ring being optionally condensed with a carbon ring or other heterocyclic ring.

Examples include pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine and the like.

As used herein, "1 to 4 carbons" means a carbon number per a single substituent; for example, for dialkyl substitution it means 2 to 8 carbons.

A halogen may be fluorine, chlorine, bromine or iodine.

An alkyl having 1 to 4 carbons includes methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl.

An alkoxy having 1 to 4 carbons includes methoxy, ethoxy, *n*-propoxy, isopropoxy, allyloxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy and the like.

An alkylamino having 1 to 4 carbons includes *N*-methylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-methyl-*N*-ethylamino, *N,N*-diisopropylamino and the like.

An acyl having 1 to 4 carbons includes acetyl, propanoyl, butanoyl and the like.

An acylamino having 1 to 4 carbons includes acetylamino, propanoylamino, butanoylamino and the like.

An alkylthio having 1 to 4 carbons includes methylthio, ethylthio, *n*-propylthio and the like.

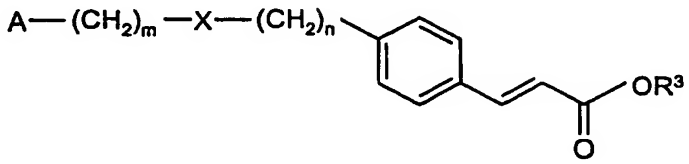
A perfluoroalkyl having 1 to 4 carbons includes trifluoromethyl, pentafluoroethyl and the like.

A perfluoroalkoxy having 1 to 4 carbons includes trifluoromethoxy, pentafluoroethoxy and the like.

An alkoxycarbonyl having 1 to 4 carbons includes methoxycarbonyl, ethoxycarbonyl and the like.

An optionally substituted alkyl having 1 to 4 carbons includes methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl and these having 1 to 4 substituents selected from the group consisting of a halogen, hydroxy, amino, nitro, cyano, phenyl and a heterocycle.

Compounds of the general formula (1) may be prepared from compounds of the general formula (3):

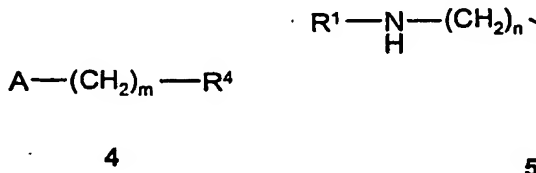


3

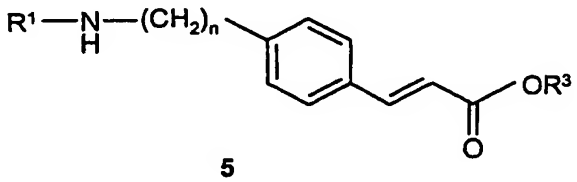
wherein A, m, X, and n are as defined above; R^3 is H or an alkyl group having 1 to 4 carbons. The reaction (when R^3 is an alkyl group having 1 to 4 carbons) is generally carried out at from 0 °C to room temperature for 1–24 hours in a suitable solvent such as a C_1–C_3 alkanol, dichloromethane, or *N*,*N*-dimethylformamide (DMF), using an excess amount of hydroxyamine salt in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, or potassium *tert*-butoxide. The reaction (when R^3 is H) may be also carried out with a carboxylic acid activator to give a reactive derivative and allowed to react with an excess amount of hydroxyamine salt under anhydrous conditions at from 0 °C to room temperature for 1–24 hours in a suitable solvent such as tetrahydrofuran (THF), acetone, dichloromethane, or DMF, in the presence of a base such as triethylamine, pyridine,

sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate. The carboxylic acid activators include thionyl chloride, phosphorous pentachloride, phosphorous oxychloride, oxalyl chloride and the like.

Compounds of the general formula (3) may be prepared from compounds of the general formula (4) and (5):



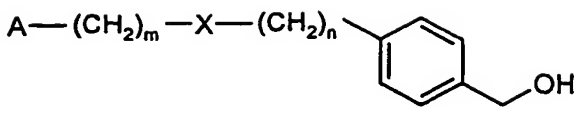
4



5

wherein A, m, R^1, n, and R^3 are as defined above; R^4 is OH or CO_2H. The coupling reaction (when R^4 is OH) is generally effected by using a well-known reagent in the literature, preferably 1,1-carbonyldiimidazole (CDI) or triphosgen, in the presence of an organic tertiary amine such as triethylamine, optionally in the presence of a catalyst such as 4-dimethylaminopyridine (DMAP), in an inert solvent such as THF, acetonitrile, dichloromethane or DMF, at from 0°C to room temperature for 2–24 hours. The coupling reaction (when R^4 is CO_2H) is generally effected by using an excess amount of a well-known reagent in the literature, preferably 1,3-dicyclohexylcarbodiimide (DCC), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), in the presence of an excess of 1-hydroxybenzotriazole, optionally in the presence of a catalyst such as DMAP, in an inert solvent such as dichloromethane or DMF, at from 0°C to room temperature for 2–24 hours. For convenience, pyridine may also be used as a solvent. The reaction may be also carried out using a carboxylic acid activator as defined above.

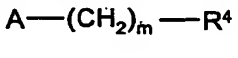
Compounds of the general formula (3) may be also prepared from compounds of the general formula (6):



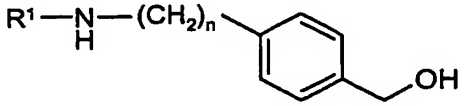
6

wherein A, m, X, and n are as defined above. The reaction is generally carried out by first converting a compound of the formula (6) to the corresponding aldehyde using well-known methods in the literature, preferably Swern oxidation, and then the aldehyde is subjected to the Wittig reaction.

Compounds of the general formula (6) may be prepared from compounds of the general formulas (7) and (8):



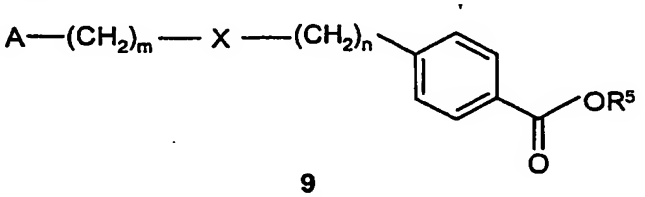
7



8

wherein A, m, R^1, R^4, and n are as defined above. The reaction is generally carried out under the same conditions as in the coupling reaction above.

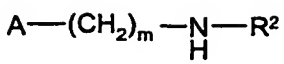
Compounds of the general formula (6) may be also prepared from compounds of the general formula (9):



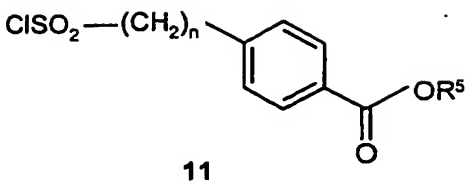
9

wherein A, m, X, and n are as defined above; R^5 is an alkyl group having 1 to 4 carbons. The reduction reaction is generally carried out under an anhydrous condition using a well-known reducing agent in the literature, preferably $LiAlH_4$ or diisobutylaluminum hydride (DIBAL-H), at from 0°C to reflux temperature for 1–24 hours.

Compounds of the general formula (9) may be prepared from compounds of the general formulas (10) and (11):



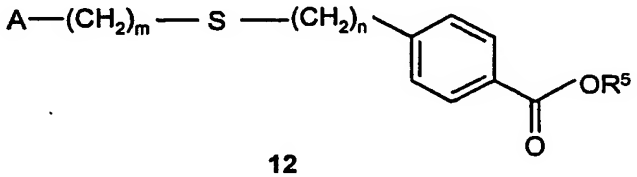
10



11

wherein A, m, R^2, n and R^5 are as defined above. The coupling reaction is generally carried out at from 0 °C to room temperature for 1–24 hours in a suitable solvent such as a C_1–C_4 alkanol, dichloromethane, DMF, or water using an excess amount of (10) or in the presence of an organic tertiary amine such as triethylamine or an inorganic base such as potassium carbonate, to scavenge the acid by-product.

Compounds of the general formula (9) may be also prepared from compounds of

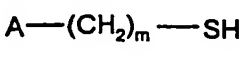


12

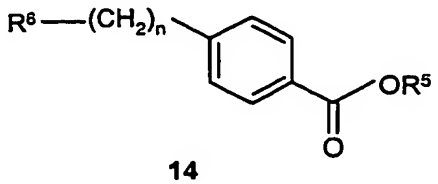
the general formula (12):

wherein A, m, n and R^5 are as defined above. The oxidation reaction is generally effected by using an excess amount of a well-known reagent in the literature, preferably OXONE, in a solvent such as aqueous C_1–C_4 alkanol, at from 0°C to room temperature for 2–24 hours.

Compounds of the general formula (12) may be prepared from compounds of the general formulas (13) and (14):



13



14

wherein A, m, n and R^5 are as defined above; R^6 represents a halogen atom, preferably a chlorine atom. The alkylation reaction is generally carried out under standard conditions in the presence of a base such as potassium carbonate or potassium *tert*-butoxide, in a suitable solvent such as DMF, at room temperature to 100°C for 2–24 hours.

Compounds represented by formula (1) may be purified or isolated by a usual separation method such as extraction, recrystallization, column chromatography and the like.

Compounds of this invention can be orally or parenterally administered. In case of oral administration, compounds of this invention may be formulated into solid formulations such as tablets, powders, granules, capsules and the like; solutions; oily suspensions; or liquid formulations such as syrups, elixirs and the like. In case of parenteral administration, compounds of this invention may be formulated into aqueous or oily suspension for injection. In preparing the formulations, conventional excipients, binders, lubricants, aqueous solvents, oily solvents, emulsifiers, suspending agents or the like may be used, and other additives, such as preservatives, stabilizers or the like may be also included.

Although appropriate daily dosages of the compounds of this invention vary depending upon the administration route, age, body weight and conditions of the patient, and the kind of disease to be treated, they can generally be between 0.05–1000 mg, preferably 10–1000 mg on oral administration, and 0.01–300 mg, preferably 0.05–100 mg on parenteral administration, in 1–5 divisions.

The following Examples are provided to further illustrate this invention and are not to be constructed as limiting thereof.

EXAMLPES

Examlpe 1

N-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-(4-pyridin-3-ylmethylpiperazin-1-yl)benzamide

(1-1) 4-(4-Pyridin-3-ylmethylpiperazin-1-yl)benzonitrile

A suspension of 1-(pyridin-3-ylmethyl)piperazine (549 mg, 3.10 mmol), 4-fluorobenzonitrile (375 mg. 3.10 mmol), and K_2CO_3 (643 mg, 4.65 mmol) in DMF (50 mL) was stirred at 80°C overnight. The reaction mixture was cooled to room temperature and filtered, and the filtrate was washed with ethyl acetate (30 mL). The combined filtrate and washings were evaporated to dryness under reduced pressure. The crude residue was purified by MPLC on silica gel (3% MeOH in CH_2Cl_2) to afford the titled compound (326 mg, 38%) as a yellow solid.

^{1}H NMR ($CDCl_3$/TMS) δ 2.59 (apparent t, 4 H, J = 5.1 Hz), 3.33 (apparent t, 4 H, J = 5.1 Hz), 3.57 (s, 2H), 6.85 (m, 2H), 7.27 (m, 1H), 7.48 (m, 2H), 7.69 (m, 1H), 8.53 (m, 1H), 8.57 (m, 1H)

(1-2) 3-(4-{[4-(4-Pyridin-3-ylmethylpiperazin-1-yl)benzoylamino]methyl}phenyl)acrylic acid ethyl ester

A solution of the compound (330 mg, 1.19 mmol) from the process (1-1) in conc. HCl (20 mL) was stirred at 80°C overnight. The reaction mixture was cooled to room temperature and then evaporated to dryness under reduced pressure. The residue was dissolved in saturated LiOH solution (pH 9) and then evaporated to dryness under reduced pressure. The residue was dissolved in 10% aqueous HCl solution (pH 2), evaporated, and dried under vacuum to give the corresponding acid, which was used in the next step without further purification.

To a mixture of the acid above, 3-(4-aminomethylphenyl)acrylic acid ethyl ester hydrochloride (287 mg, 1.19 mmol), 1-hydroxybenzotriazole (240 mg, 1.78 mmol), and

DMAP (29 mg, 0.24 mmol) in pyridine (20 mL) was added EDC (341 mg, 1.78 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and to it an aqueous $NaHCO_3$ solution (20 mL) was added. The mixture was extracted with 5% MeOH in CH_2Cl_2 (30 mL x 3), and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by MPLC on silica gel (4% MeOH in CH_2Cl_2) to afford the titled compound (482 mg, 84%) as a pale yellow solid.

^{1}H NMR ($CDCl_3$/TMS) δ 1.34 (t, 3H, J = 7.2 Hz), 2.60 (apparent t, 4H, J = 5.1 Hz), 3.30 (apparent t, 4H, J = 5.1 Hz), 3.57 (s, 2H), 4.26 (q, 2H, J = 7.2 Hz), 4.64 (d, 2H, J = 5.7 Hz), 6.32 (br t, 1H, J = 5.7 Hz), 6.41 (d, 1H, J = 15.9 Hz), 6.88 (m, 2H), 7.27 (m, 1H), 7.36 (d, 2H, J = 8.1 Hz), 7.49 (d, 2H, J = 8.1 Hz), 7.64–7.72 (m, 4H), 8.53 (m, 1H), 8.57 (m, 1H)

(1-3) *N*-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-(4-pyridin-3-ylmethylpiperazin-1-yl)benzamide

To a solution of 1.76 M NH_2OH in MeOH (1.23 mL) was added the compound (150 mg, 0.31 mmol) from the process (1-2), and the mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated, and the residue was dissolved in 1 N HCl aqueous solution (pH 5). The solid precipitated was collected by filtration, dried under vacuum, and crystallized from MeOH/CH_2Cl_2/ether to afford the titled compound (67 mg, 46%) as a pale brown solid.

^{1}H NMR (DMSO-d_6) δ 2.56 (m, 4H), 3.28 (m, 4H), 3.62 (br s, 2H), 4.45 (d, 2H, J = 5.7 Hz), 6.42 (d, 1H, J = 15.9 Hz), 6.96 (m, 2H), 7.31 (d, 2H, J = 8.1 Hz), 7.37–7.45 (m, 2H), 7.50 (d, 2H, J = 8.1 Hz), 7.76–7.79 (m, 3H), 8.50 (m, 1H), 8.54 (m, 1H), 8.78 (br t, 1H, J =5.7 Hz), 9.01 (br s, 1H), 10.73 (br s, 1H)

Example 2

N-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-(4-pyridin-2-ylmethylpiperazin-1-yl)benzamide

The titled compound was prepared as described in Example 1 by using 1-(pyridin-2-ylmethyl)piperazine in place of 1-(pyridin-3-ylmethyl)piperazine.

(2-1) 4-(4-Pyridin-2-ylmethylpiperazin-1-yl)benzonitrile

yield: 32% (yellow solid)

^{1}H NMR ($CDCl_3$/TMS) δ 2.66 (apparent t, 4H, J = 5.1 Hz), 3.36 (apparent t, 4H, J = 5.1 Hz), 3.72 (s, 2H), 6.84 (m, 2H), 7.19 (m, 1H), 7.42 (m, 1H,), 7.48 (m, 2H), 7.68 (m, 1H), 8.59 (m, 1H)

(2-2) 3-(4-{[4-(4-Pyridin-2-ylmethylpiperazin-1-yl)benzoylamino]methyl}phenyl)acrylic acid ethyl ester

yield: 38% (off-white solid)

^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz), 2.57 (m, 4H), 3.28 (m, 4H), 3.66 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 4.46 (d, 2H, J = 5.7 Hz), 6.59 (d, 1H, J = 16.2 Hz), 6.96 (m, 2H), 7.26–7.34 (m, 3H), 7.48 (m, 1H), 7.60–7.68 (m, 3H), 7.75–7.81 (m, 3H), 8.51 (m, 1H), 8.80 (br t, 1H, J =5.7 Hz)

(2-3) *N*-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-(4-pyridin-2-ylmethylpiperazin-1-yl)benzamide

yield: 59% (off-pink solid)

^{1}H NMR (DMSO-d_6) δ 2.59 (m, 4H), 3.28 (m, 4H), 3.68 (br s, 2H), 4.45 (d, 2H, J = 5.7 Hz), 6.42 (d, 1H, J = 15.9 Hz), 6.96 (m, 2H), 7.26–7.34 (m, 3H), 7.43 (d, 1H, J = 15.9 Hz), 7.47–7.52 (m, 3H), 7.77–7.81 (m, 3H), 8.51 (m, 1H), 8.78 (br t, 1H, J =5.7 Hz), 9.02 (br s, 1H), 10.73 (br s, 1H)

Example 3

N-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-(4-pyridin-4-ylmethylpiperazin-1-yl)benzamide

The titled compound was prepared as described in Example 1 by using 1-(pyridin-4-ylmethyl)piperazine in place of 1-(pyridin-3-ylmethyl)piperazine.

(3-1) 4-(4-Pyridin-4-ylmethylpiperazin-1-yl)benzonitrile

yield: 59% (yellow solid)

^{1}H NMR ($CDCl_3$/TMS) δ 2.59 (apparent t, 4H, J = 5.1 Hz), 3.35 (apparent t, 4H, J = 5.1 Hz), 3.56 (s, 2H), 6.85 (m, 2H), 7.30 (m, 2H), 7.49 (m, 2H), 8.56 (m, 2H)

(3-2) 3-(4-{[4-(4-Pyridin-4-ylmethylpiperazin-1-yl)benzoylamino]methyl}phenyl)acrylic acid ethyl ester

yield: 94% (off-white solid)

^{1}H NMR ($CDCl_3$/TMS) δ 1.33 (t, 3H, J = 7.2 Hz), 2.60 (apparent t, 4H, J = 5.1 Hz), 3.31 (apparent t, 4H, J = 5.1 Hz), 3.56 (s, 2H), 4.26 (q, 2H, J = 7.2 Hz), 4.65 (d, 2H, J = 5.7 Hz), 6.36 (br t, 1H, J = 5.7 Hz), 6.41 (d, 1H, J = 15.9 Hz), 6.88 (m, 2H), 7.30 (d, 2H, J = 6.0 Hz), 7.36 (d, 2H, J = 8.1 Hz), 7.49 (d, 2H, J = 8.1 Hz), 7.66 (d, 1H, J = 15.9 Hz), 7.72 (m, 2H) 8.56 (m, 2H)

(3-3) *N*-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-(4-pyridin-4-ylmethylpiperazin-1-yl)benzamide

yield: 54% (pale brown solid)

^{1}H NMR (DMSO-d_6) δ 2.52 (m, 4H), 3.28 (m, 4H), 3.57 (s, 2H), 4.45 (d, 2H, J = 5.7 Hz), 6.42 (d, 1H, J = 15.9 Hz), 6.96 (m, 2H), 7.32 (d, 2H, J = 8.1 Hz), 7.36 (d, 2H, J = 6.0 Hz), 7.42 (d, 1H, J = 15.9 Hz), 7.51 (d, 2H, J = 8.1 Hz), 7.78 (m, 2H), 8.53 (d, 2H, J = 6.0 Hz), 8.78 (br t, 1H, J =5.7 Hz), 9.02 (br s, 1H), 10.73 (br s, 1H)

Example 4

N-[4-(2-Hydroxycarbamoylvinyl)benzyl]picolinamide

The titled compound was prepared in a similar manner to the process described in Example 1 by using picolinic acid.

(4-1) 3-{4-[(Picolinoylamino)methyl]phenyl}acrylic acid ethyl ester

yield: 58% (pale yellow oil)

^{1}H NMR ($CDCl_3$/TMS) δ 1.34 (t, 3H, J = 7.2 Hz), 4.26 (q, 2H, J = 7.2 Hz), 4.69 (d, 2H, J = 6.3 Hz), 6.42 (d, 1H, J = 15.9 Hz), 7.38 (d, 2H, J = 8.1 Hz), 7.44 (m, 1H), 7.50 (d, 2H, J = 8.1 Hz), 7.67 (d, 1H, J = 15.9 Hz), 7.87 (m, 1H), 8.24 (m, 1H), 8.42 (m, 1H), 8.54 (m, 1H)

(4-2) *N*-[4-(2-Hydroxycarbamoylvinyl)benzyl]picolinamide

yield: 29% (off-white solid)

^{1}H NMR (DMSO-d_6) δ 4.51 (m, 2H), 6.45 (d, 1H, J = 15.9 Hz), 7.35 (d, 2H, J = 8.1 Hz), 7.42 (d, 1H, J = 15.9 Hz), 7.50 (d, 2H, J = 8.1 Hz), 7.59–7.64 (m, 1H), 7.97–8.06 (m, 2H), 8.66 (m, 1H), 9.02 (br s, 1H), 9.36 (m, 1H), 10.76 (br s, 1H)

Example 5

N-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-pyrrolidin-1-ylbenzamide

(5-1) *N*-(4-Hydroxymethylbenzyl)-4-pyrrolidin-1-ylbenzamide

To a mixture of 4-pyrrolidin-1-ylbenzoic acid (2.0 g, 10.5 mmol), (4-aminomethylphenyl)methanol (4.3 g, 31.4 mmol), 1-hydroxybenzotriazole (1.7 g, 12.6 mmol), and DMAP (256 mg, 2.1 mmol) in pyridine (50 mL) was added EDC (3.0 g, 15.7 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and an aqueous $NaHCO_3$ solution (50

mL) was added. The mixture was extracted with 5% MeOH in $CHCl_3$ (150 mL x 2), and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by MPLC on silica gel (3% MeOH in $CHCl_3$) to afford the titled compound (2.56 g, 79%) as a white solid.

^1H NMR (DMSO-d_6) δ 1.96 (m, 4H), 3.28 (m, 4H), 4.41–4.47 (m, 4H), 5.10 (t, 1H, J = 5.7 Hz), 6.53 (m, 2H), 7.25 (apparent s, 4H), 7.75 (m, 2H), 8.59 (br t, 1H, J=6.0 Hz)

(5-2) 3-{4-[(4-Pyrrolidin-1-ylbenzoylamino)methyl]phenyl}acrylic acid ethyl ester

To a solution of oxalyl chloride (0.93 mL, 10.6 mmol) in THF (10 mL) at –78°C was added a solution of DMSO (1.65 mL, 23.2 mmol) in THF (10 mL), and the reaction mixture was stirred for 30 minutes. A solution of the compound (1.5 g, 4.8 mmol) from the process (5-1) in THF (200 mL) was added to it, and then the mixture was stirred for 1 hour and warmed to –35°C. After 10 minutes, the mixture was cooled to –78 °C, and triethylamine (3.37 mL, 24.2 mmol) was added. After stirring at 0 °C for 1 hour, the mixture was diluted with water (150 mL), and then THF was evaporated under reduced pressure. The resulting residue was extracted with 5% MeOH in $CHCl_3$ (250 mL x 2). The extract was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give a crude product which was crystallized from MeOH/ $CHCl_3$/ether to afford the corresponding aldehyde (925 mg, 62%) as a white solid.

A solution of the aldehyde (1.35 g, 4.38 mmol) above, $(Ph)_3P{=}CHCO_2Et$ (2.29 g, 6.57 mmol) in CH_3CN (60 mL) was stirred at 70 °C for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by MPLC on silica gel (2% MeOH in $CHCl_3$) to afford the titled compound (1.25 g, 76%) as a pale yellow solid.

^1H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz), 1.96 (m, 4H), 3.28 (m, 4H), 4.18 (q, 2H, J = 7.2 Hz), 4.46 (d, 2H, J = 5.7 Hz), 6.54 (m, 2H), 6.58 (d, 1H, J = 16.5 Hz), 7.33 (d, 2H, J = 8.1 Hz), 7.62 (d, 1H, J = 16.5 Hz), 7.67 (d, 2H, J = 8.1 Hz), 7.76 (m, 2H), 8.66

(br t, 1H, J = 5.7 Hz)

(5-3) *N*-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-pyrrolidin-1-ylbenzamide

The titled compound was prepared as described in the process (1-3) by using the compound from the process (5-2).

yield: 35% (pale brown solid)

^{1}H NMR (DMSO-d_6) δ 1.96 (m, 4H), 3.28 (m, 4H), 4.45 (d, 2H, J = 5.7 Hz), 6.42 (d, 1H, J = 15.9 Hz), 6.54 (m, 2H), 7.32 (d, 2H, J = 8.1 Hz), 7.43 (d, 1H, J = 15.9 Hz), 7.50 (d, 2H, J = 8.1 Hz), 7.76 (m, 2H), 8.64 (br t, 1H, J = 5.7 Hz), 9.00 (br s, 1H), 10.70 (br s, 1H)

Example 6

4-Dimethylamino-*N*-[4-(2-hydroxycarbamoylvinyl)benzyl]benzamide

The titled compound was prepared as described in Example 5 by using 4-(dimethylamino)benzoic acid in place of 4-pyrrolidin-1-ylbenzoic acid.

(6-1) 4-Dimethylamino-*N*-(4-hydroxymethylbenzyl)benzamide

To a mixture of 4-(dimethylamino)benzoic acid (915 mg, 5.54 mmol) and triethylamine (772μL, 5.54 mmol) in CH_2Cl_2 (25 mL) at 0°C was added BOP-Cl (1.50 g, 6.09 mmol), and the mixture was stirred at room temperature for 20 minutes. To the reaction mixture was added (4-aminomethylphenyl)methanol (760 mg, 5.54 mmol) and triethylamine (1.54mL, 11.08 mmol), and the mixture was stirred at room temperature overnight. To the reaction mixture was added a 50% aqueous $NaHCO_3$ solution (50 mL), and the mixture was extracted with 5% MeOH in $CHCl_3$ (100 mL x 1, 40 mL x 2). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by MPLC on silica gel (2% MeOH in $CHCl_3$) to afford the titled compound (1.04 g, 66%) as a white solid.

^{1}H NMR (DMSO-d_6) δ 2.97 (s, 6H), 4.41–4.47 (m, 4H), 5.10 (t, 1H, J = 5.7 Hz), 6.70 (m, 2H), 7.25 (apparent s, 4H), 7.76 (m, 2H), 8.63 (br t, 1H, J =6.0 Hz)

(6-2) 3-{4-[(4-Dimethylaminobenzoylamino)methyl]phenyl}acrylic acid ethyl ester

yield: 74% (white solid)

^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz), 2.97 (s, 6H), 4.18 (q, 2H, J = 7.2 Hz), 4.46 (d, 2H, J = 6.0 Hz), 6.59 (d, 1H, J = 15.9 Hz), 6.71 (m, 2H), 7.33 (d, 2H, J = 8.1 Hz), 7.63 (d, 1H, J = 15.9 Hz), 7.67 (d, 2H, J = 8.1 Hz), 7.77 (m, 2H), 8.70 (br t, 1H, J = 6.0 Hz)

(6-3) 4-Dimethylamino-*N*-[4-(2-hydroxycarbamoylvinyl)benzyl]benzamide

yield: 58% (pale pink solid)

^{1}H NMR (DMSO-d_6) δ 2.97 (s, 6H), 4.45 (d, 2H, J = 5.7 Hz), 6.42 (d, 1H, J = 15.9 Hz), 6.71 (m, 2H), 7.33 (d, 2H, J = 8.1 Hz), 7.43 (d, 1H, J = 15.9 Hz), 7.51 (d, 2H, J = 8.1 Hz), 7.77 (m, 2H), 8.68 (br t, 1H, J = 5.7 Hz), 9.00 (br s, 1H), 10.71 (br s, 1H)

Example 7

N-[4-(2-Hydroxycarbamoylvinyl)benzyl]nicotinamide

The titled compound was prepared as described in Example 5 by using nicotinic acid in place of 4-pyrrolidin-1-ylbenzoic acid.

(7-1) *N*-(4-Hydroxymethylbenzyl)nicotinamide

yield: 86% (white solid)

^{1}H NMR (DMSO-d_6) δ 4.46–4.49 (m, 4H), 5.13 (br t, 1H, J = 5.6 Hz), 7.28 (apparent s, 4H), 7.51 (dd, 1H, J = 7.8 Hz, 4.8 Hz), 8.22 (m, 1H), 8.71 (dd, 1H, J = 4.8 Hz, 1.5 Hz), 9.04 (d, 1H, J = 2.1 Hz), 9.21 (br t, 1H, J = 5.7 Hz)

(7-2) 3-{4-[(Nicotinoylamino)methyl]phenyl}acrylic acid ethyl ester

yield: 39% (pale yellow solid)

^{1}H NMR (DMSO-d_6) δ 1.26 (t, 3H, J = 7.2 Hz), 4.19 (q, 2H, J = 7.2 Hz), 4.53 (d, 2H, J = 6.0 Hz), 6.60 (d, 1H, J = 15.9 Hz), 7.38 (d, 2H, J = 8.1 Hz), 7.52 (m, 1H), 7.63 (d, 1H, J = 15.9 Hz), 7.69 (d, 2H, J = 8.1 Hz), 8.23 (m, 1H), 8.72 (m, 1H), 9.06 (m, 1H), 9.26 (br t, 1H, J = 6.0 Hz)

(7-3) *N*-[4-(2-Hydroxycarbamoylvinyl)benzyl]nicotinamide

yield: 74% (pale pink solid)

^{1}H NMR (DMSO-d_6) δ 4.51 (m, 2H), 6.43 (d, 1H, J = 15.9 Hz), 7.37 (d, 2H, J = 8.1 Hz), 7.44 (d, 1H, J = 15.9 Hz), 7.52 (m, 1H), 7.53 (d, 2H, J = 8.1 Hz), 8.23 (m, 1H), 8.72 (m, 1H), 9.05 (m, 1H), 9.25 (m, 1H)

Example 8

[4-(2-Hydroxycarbamoylvinyl)benzyl]carbamic acid pyridin-3-ylmethyl ester

(8-1) (4-Hydroxymethylbenzyl)carbamic acid pyridin-3-ylmethyl ester

To a solution of *N*,*N*-carbonyldiimidazole (2.1 g, 12.8 mmol) in THF (15 mL) was added a solution of 3-pyridylcarbinol (1.3 g, 11.6 mmol) in THF (15 mL). After stirring for 30 minutes, a solution of (4-aminomethylphenyl)methanol (1.4 g, 10.4 mmol) in THF (15 mL) and triethylamine (3.2 mL, 23.2 mmol) were added, and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with water (30 mL) and extracted with 10% MeOH in $CHCl_3$ (30 mL x 2). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure, and the residue was purified by MPLC on silica gel (5% MeOH in $CHCl_3$) to afford the titled compound (1.31 g, 46%) as a white solid.

^{1}H NMR (DMSO-d_6) δ 4.18 (m, 2H), 4.45 (s, 2H), 5.08 (s, 2H), 7.19 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 7.40 (m, 1H), 7.77 (m, 1H), 7.83 (m, 1H), 8.52 (m, 1H), 8.58 (m, 1H)

(8-2) 3-{4-[(pyridin-3-ylmethoxycarbonylamino)methyl]phenyl}acrylic acid methyl ester

The titled compound was prepared as described in the process (5-2) using the compound from the process (8-1).

yield: 75% (white solid)

^{1}H NMR (DMSO-d_6) δ 3.72 (s, 3H), 4.23 (d, 2H, J = 6.0 Hz), 5.09 (s, 2H), 6.61 (d, 1H, J = 15.9 Hz), 7.29 (d, 2H, J = 8.1 Hz), 7.40 (m, 1H), 7.64 (d, 1H, J = 15.9 Hz), 7.67 (d, 2H, J = 8.1 Hz), 7.78 (m, 1H), 7.90 (br t, 1H, J = 6.0 Hz), 8.53 (m, 1H), 8.58 (m, 1H)

(8-3) [4-(2-Hydroxycarbamoylvinyl)benzyl]carbamic acid pyridin-3-ylmethyl ester

The titled compound was prepared as described in the process (1-3) using the compound from the process (8-2).

yield: 39% (pale pink solid)

^{1}H NMR (DMSO-d_6) δ 4.21 (m, 2H), 5.09 (s, 2H), 6.43 (d, 1H, J = 15.9 Hz), 7.28 (m, 2H), 7.40 (m, 1H), 7.43 (d, 1H, J = 15.9 Hz), 7.51 (m, 2H), 7.78 (m, 1H), 7.89 (m, 1H), 8.53 (m, 1H), 8.59 (m, 1H)

Example 9

N-Hydroxy-3-[4-(pyridin-3-ylsulfamoylmethyl)phenyl]acrylamide

(9-1) 4-(Pyridin-3-ylsulfamoylmethyl)benzoic acid methyl ester

To a solution of 4-chlorosulfonylmethylbenzoic acid methyl ester (435 mg, 1.75 mmol) and 3-aminopyridine (170 mg, 1.81 mmol) in CH_2Cl_2 (10 mL) at 0°C was added triethylamine (488μL, 3.50 mmol), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with $CHCl_3$, and the mixture was washed with water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which was purified by MPLC on silica gel

(3% MeOH in EtOAc) to afford the titled compound (434 mg, 81%) as a white solid.

^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H), 4.68 (s, 2H), 7.32 (dd, 1H, J = 8.4 Hz, 4.8 Hz), 7.45 (d, 2H, J = 8.1 Hz), 7.55 (m, 1H), 7.93 (d, 2H, J = 8.1 Hz), 8.28 (dd, 1H, J = 4.8 Hz, 1.5 Hz), 8.36 (d, 1H, J = 1.8 Hz), 10.13 (br s, 1H)

(9-2) *C*-(4-Hydroxymethylphenyl)-*N*-pyridin-3-ylmethanesulfonamide

To a solution of 4-(pyridin-3-ylsulfamoylmethyl)benzoic acid methyl ester (1.91 g, 6.23 mmol) in THF (60 mL) at 0°C was added a 1 M solution of $LiAlH_4$ in THF (13.7 mL, 13.7 mmol), and the mixture was warmed to room temperature. After stirring for 10 minutes, the mixture was heated to reflux temperature for 3 hours. The reaction mixture was cooled to 0°C and quenched with saturated Na_2SO_4 aqueous solution (1.9 mL). The mixture was neutalized with 1 N HCl solution (13.7 mL), and then THF was evaporated under reduced pressure. The residue was diluted with water (70 mL) and extracted with $CHCl_3$ (50mL x 3). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by MPLC on silica gel (6% MeOH in EtOAc) to afford the titled compound (1.43 g, 83%) as a pale yellow solid.

^{1}H NMR (DMSO-d_6) δ 4.48 (s, 2H), 4.50 (s, 2H), 7.22 (d, 2H, J = 8.1 Hz), 7.29 (d, 2H, J = 8.1 Hz), 7.32 (m, 1H), 7.55 (m, 1H), 8.26(m, 1H), 8.36(m, 1H)

(9-3) 3-[4-(Pyridin-3-ylsulfamoylmethyl)phenyl]acrylic acid ethyl ester

The titled compound was prepared as described in the process (5-2) using the compound from the process (9-2).

yield: 53% (white solid)

^{1}H NMR (DMSO-d_6) δ 1.27 (t, 3H, J = 7.2 Hz), 4.20 (q, 2H, J = 7.2 Hz), 4.60 (s, 2H), 6.64 (d, 1H, J = 15.9 Hz), 7.31 (m, 1H), 7.33 (d, 2H, J = 8.1 Hz), 7.55 (m, 1H), 7.63 (d, 1H, J = 15.9 Hz), 7.70 (d, 2H, J = 8.1 Hz), 8.27 (m, 1H), 8.36 (m, 1H), 10.20 (br s, 1H)

(9-4) *N*-Hydroxy-3-[4-(pyridin-3-ylsulfamoylmethyl)phenyl]acrylamide

The titled compound was prepared as described in the process (1-3) using the compound from the process (9-3).

yield: 64% (white solid)

^{1}H NMR (DMSO-d_6) δ 4.59 (s, 2H), 6.46 (d, 1H, J = 15.9 Hz), 7.30–7.34 (m, 3H), 7.44 (d, 1H, J = 15.9 Hz), 7.52–7.57 (m, 3H), 8.28 (m, 1H), 8.37 (m, 1H), 9.04 (br s, 1H), 10.08 (br s, 1H), 10.75 (br s, 1H)

Example 10

3-[4-(Benzenesulfonylmethyl)phenyl]-*N*-hydroxyacrylamide

(10-1) 4-(Phenylsulfanylmethyl)benzoic acid methyl ester

To a mixture of benzenethiol (1.3 mL, 13.1 mmol) and potassium *tert*-butoxide (1.47 g, 13.1 mmol) in DMF (50 mL) at 0°C was added 4-(bromomethyl)benzoic acid methyl ester (3.0 g, 13.1 mmol), and the mixture was stirred at room temperature for 1 hour. After stirring at 80-90°C overnight, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in water (30 mL) and extracted with CH_2Cl_2 (200 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by MPLC on silica gel (10% EtOAc in hexanes) to afford the titled compound (2.74 g, 81%) as a white solid.

^{1}H NMR ($CDCl_3$/TMS) δ 3.90 (s, 3H), 4.12 (s, 2H), 7.19–7.30 (m, 5H), 7.32 (d, 2H, J = 8.1 Hz), 7.94 (d, 2H, J = 8.1 Hz)

(10-2) 4-(Benzenesulfonylmethyl)benzoic acid methyl ester

To a mixture of the compound (2.5 g, 9.68 mmol) from the process (10-1) in a 50 % aqueous solution of methanol (60 mL) at 0°C was added OXONE (12.5 g, 20.32 mmol), and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous $NaHCO_3$ solution (25 mL), and the mixture was

extracted with CH_2Cl_2 (250 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by MPLC on silica gel (1% MeOH in $CHCl_3$) to afford the titled compound (2.36 g, 84%) as a white solid.

^{1}H NMR ($CDCl_3$/TMS) δ 3.84 (s, 3H), 4.81 (s, 2H), 7.29 (d, 2H, J = 8.1 Hz), 7.57–7.62 (m, 2H), 7.69–7.72 (m, 3H), 7.86 (d, 2H, J = 8.1 Hz)

(10-3) [4-(Benzenesulfonylmethyl)phenyl]methanol

To a solution of the compound (2.3 g, 7.92 mmol) from the process (10-2) in CH_2Cl_2 (50 mL) at –78°C was added slowly DIBAL-H (1 M in toluene, 16.6 mL, 16.63 mmol), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to 0°C, and to it an aqueous NH_4Cl solution (250 mL) was added slowly. The mixture was extracted with 10% MeOH in CH_2Cl_2 (1.5 L), and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was crystallized from MeOH/CH_2Cl_2/ether to afford the titled compound (1.66 g, 80%) as white solid.

^{1}H NMR (DMSO-d_6) δ 4.45 (s, 2H), 4.64 (s, 2H), 7.08 (d, 2H, J = 8.1 Hz), 7.21 (d, 2H, J = 8.1 Hz), 7.56–7.61 (m, 2H), 7.69–7.73 (m, 3H)

(10-4) 3-[4-(Benzenesulfonylmethyl)phenyl]acrylic acid ethyl ester

The titled compound was prepared as described in the process (5-2) using the compound from the process (10-3).

yield: 82% (white solid)

^{1}H NMR (DMSO-d_6) δ 3.72 (s, 3H), 4.73 (s, 2H), 6.64 (d, 1H, J = 15.9 Hz), 7.18 (d, 2H, J = 8.1 Hz), 7.57–7.65 (m, 5H), 7.70–7.74 (m, 3H)

(10-5) 3-[4-(Benzenesulfonylmethyl)phenyl]-*N*-hydroxyacrylamide

The titled compound was prepared as described in the process (1-3) using the compound from the process (10-4).

yield: 52% (pale red solid)

^{1}H NMR (DMSO-d_6) δ 4.71 (s, 2H), 6.45 (d, 1H, J = 15.9 Hz), 7.17 (d, 2H, J = 8.1 Hz), 7.41 (d, 1H, J = 15.9 Hz), 7.47 (d, 2H, J = 8.1 Hz), 7.57–7.62 (m, 2H), 7.71–7.74 (m, 3H), 9.04 (br s, 1H), 10.75 (br s, 1H)

Example 11

N-Hydroxy-3-[4-(pyridine-2-sulfonylmethyl)phenyl]acrylamide

The titled compound was prepared as described in Example 10 by using 2-mercaptopyridine in place of benzenethiol.

(11-1) 4-(Pyridine-2-sulfanylmethyl)benzoic acid methyl ester

yield: 76% (white solid)

^{1}H NMR ($CDCl_3$/TMS) δ 3.89 (s, 3H), 4.48 (s, 2H), 6.99 (m, 1H), 7.15 (m, 1H), 7.44–7.50 (m, 3H), 7.95 (d, 2H, J = 8.1 Hz), 8.45 (m, 1H)

(11-2) 4-(Pyridine-2-sulfonylmethyl)benzoic acid methyl ester

yield: 98% (white solid)

^{1}H NMR ($CDCl_3$/TMS) δ 3.83 (s, 3H), 4.94 (s, 2H), 7.34 (d, 2H, J = 8.4 Hz), 7.76 (m, 1H), 7.84 (m, 1H), 7.86 (d, 2H, J = 8.4 Hz), 8.07 (m, 1H), 8.85 (m, 1H)

(11-3) [4-(Pyridine-2-sulfonylmethyl)phenyl]methanol

yield: 79% (white solid)

^{1}H NMR (DMSO-d_6) δ 4.44 (s, 2H), 4.78 (s, 2H), 7.12 (d, 2H, J = 8.1 Hz), 7.21 (d, 2H, J = 8.1 Hz), 7.75 (m, 1H), 7.84 (m, 1H), 8.07 (m, 1H), 8.86 (m, 1H)

(11-4) 3-[4-(Pyridine-2-sulfonylmethyl)phenyl]acrylic acid methyl ester

yield: 84% (pale yellow solid)

^{1}H NMR (DMSO-d_6) δ 3.72 (s, 3H), 4.87 (s, 2H), 6.63 (d, 1H, J = 15.8 Hz), 7.23 (d, 2H, J = 8.1 Hz), 7.61 (d, 1H, J = 15.8 Hz), 7.64 (d, 2H, J = 8.1 Hz), 7.76 (m, 1H), 7.86 (m, 1H), 8.08 (m, 1H), 8.86 (m, 1H)

(11-5) *N*-Hydroxy-3-[4-(pyridine-2-sulfonylmethyl)phenyl]acrylamide

yield: 42% (pale red solid)

^{1}H NMR (DMSO-d_6) δ 4.85 (s, 2H), 6.43 (d, 1H, J = 16.2 Hz), 7.21 (d, 2H, J = 8.1 Hz), 7.40 (d, 1H, J = 16.2 Hz), 7.47 (d, 2H, J = 8.1 Hz), 7.76 (m, 1H), 7.85 (m, 1H), 8.08 (m, 1H), 8.86 (m, 1H), 9.04 (br s, 1H), 10.74 (br s, 1H)

Example 12

N-Hydroxy-3-[4-(pyridine-4-sulfonylmethyl)phenyl]acrylamide

The titled compound was prepared as described in Example 10 by using 4-mercaptopyridine in place of benzenethiol.

(12-1) 4-(Pyridine-4-sulfanylmethyl)benzoic acid methyl ester

yield: 77% (pale yellow solid)

^{1}H NMR ($CDCl_3$/TMS) δ 3.91 (s, 3H), 4.24 (s, 2H), 7.09 (m, 1H), 7.47 (d, 2H, J = 8.1 Hz), 8.01 (d, 2H, J = 8.1 Hz), 8.38 (m, 1H)

(12-2) 4-(Pyridine-4-sulfonylmethyl)benzoic acid methyl ester

yield: 71% (white solid)

^{1}H NMR ($CDCl_3$/TMS) δ 3.93 (s, 3H), 4.39 (s, 2H), 7.20 (d, 2H, J = 8.1 Hz), 7.48 (m, 1H), 7.97 (d, 2H, J = 8.1 Hz), 8.81 (m, 1H)

(12-3) [4-(Pyridine-4-sulfonylmethyl)phenyl]methanol

yield: 69% (white solid)

^{1}H NMR (DMSO-d_6) δ 4.46 (s, 2H), 4.74 (s, 2H), 7.13 (d, 2H, J = 8.1 Hz), 7.24 (d, 2H, J = 8.1 Hz), 7.70 (m, 2H), 8.87 (m, 2H)

(12-4) 3-[4-(Pyridine-4-sulfonylmethyl)phenyl]acrylic acid ethyl ester

yield: 51% (white solid)

^{1}H NMR (DMSO-d_6) δ 1.34 (t, 3H, J = 7.2 Hz), 4.27 (q, 2H, J = 7.2 Hz), 4.36 (s, 2H),

6.44 (d, 1H, J = 15.9 Hz), 7.15 (d, 2H, J = 8.1 Hz), 7.45 (d, 2H, J = 8.1 Hz), 7.50 (m, 2H), 7.64 (d, 1H, J = 15.9 Hz), 8.82 (m, 2H)

(12-5) *N*-Hydroxy-3-[4-(pyridine-4-sulfonylmethyl)phenyl]acrylamide

yield: 45% (red solid)

^{1}H NMR (DMSO-d_6) δ 4.88 (s, 2H), 6.46 (d, 1H, J = 15.3 Hz), 7.21 (d, 2H, J = 8.1 Hz), 7.36 (d, 1H, J = 15.3 Hz), 7.49 (d, 2H, J = 8.1 Hz), 7.70 (d, 1H, J = 5.4 Hz), 8.88 (d, 1H, J = 5.4 Hz), 9.07 (br s, 1H), 10.76 (br s, 1H)

Example 13

Naphthalene-2-carboxylic acid 4-(2-hydroxycarbamoylvinyl)benzylamide

(13-1) 3-(4-{[(Naphthalene-2-carbonyl)amino]methyl}phenyl)acrylic acid ethyl ester

The titled compound was prepared as described in the process (1-2) by using 2-naphthoic acid.

yield: 82% (white solid)

^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.56 (m, 2H), 7.60 (d, 1H, J = 15.9 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.57–7.71 (m, 5H), 7.97–8.05 (m, 4H), 8.51 (s, 1H), 9.24 (br t, 1H, J = 6.0 Hz)

(13-2) Naphthalene-2-carboxylic acid 4-(2-hydroxycarbamoylvinyl)benzylamide

The titled compound was prepared as described in the process (1-2) by using the compound from the process (13-1).

yield: 85% (pale pink solid)

^{1}H NMR (DMSO-d_6) δ 4.55 (m, 2H), 6.44 (d, 1H, J = 15.6 Hz), 7.38–7.65 (m, 7H), 7.97–8.04 (m, 4H), 8.51 (s, 1H), 9.23 (m, 1H)

Example 14

Quinoline-3-carboxylic acid 4-(2-hydroxycarbamoylvinyl)benzylamide

(14-1) 3-(4-{[(Quinoline-3-carbonyl)amino]methyl}phenyl)acrylic acid ethyl ester

The titled compound was prepared as described in the process (1-2) by using 3-quinolinecarboxylic acid.

yield: 89% (white solid)

^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.58 (d, 2H, J = 5.7 Hz), 6.61 (d, 1H, J = 15.9 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.64 (d, 1H, J = 15.9 Hz), 7.68–7.72 (m, 3H), 7.85–7.90 (m, 1H), 8.08–8.12 (m, 2H), 8.88 (m, 1H), 9.33 (m, 1H), 9.42 (br t, 1H, J = 5.7 Hz)

(14-2) Quinoline-3-carboxylic acid 4-(2-hydroxycarbamoylvinyl)benzylamide

The titled compound was prepared as described in the process (1-2) by using the compound from the process (14-1).

yield: 89% (pale pink solid)

^{1}H NMR (DMSO-d_6) δ 4.58 (d, 2H, J = 5.1 Hz), 6.45 (d, 1H, J = 15.9 Hz), 7.42 (d, 2H, J = 8.1 Hz), 7.43–7.56 (m, 3H), 7.70 (m, 1H), 7.88 (m, 1H), 8.10 (d, 2H, J = 8.1 Hz), 8.89 (m, 1H), 9.01 (br s, 1H), 9.33 (m, 1H), 9.42 (m, 1H), 10.74 (br s, 1H)

Example 15

Quinoline-2-carboxylic acid 4-(2-hydroxycarbamoylvinyl)benzylamide

The titled compound was prepared as described in Example 5 by using 2-quinolinecarboxylic acid in place of 4-pyrrolidin-1ylbenzoic acid.

(15-1) Quinoline-2-carboxylic acid 4-hydroxymethylbenzylamide

yield: 82% (white solid)

^{1}H NMR ($CDCl_3$/TMS) δ 1.90 (m, 1H), 4.69 (d, 2H, J = 5.1 Hz), 4.72 (d, 2H, J = 6.3

Hz), 7.35 (d, 2H, J = 8.1 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.61 (m, 1H), 7.74 (m, 1H), 7.88 (m, 1H), 8.06 (m, 1H), 8.32 (m, 2H), 8.61 (m, 1H)

(15-2) 3-(4-{[(Quinoline-2-carbonyl)amino]methyl}phenyl)acrylic acid ethyl ester

yield: 91% (white solid)

^{1}H NMR ($CDCl_3$/TMS) δ 1.34 (t, 3H, J = 7.2 Hz), 4.26 (q, 2H, J = 7.2 Hz), 4.76 (d, 2H, J = 6.3 Hz), 6.43 (d, 1H, J = 15.9 Hz), 7.43 (d, 2H, J = 8.1 Hz), 7.52 (d, 2H, J = 8.1 Hz), 7.60–7.71 (m, 2H), 7.76 (m, 1H), 7.89 (m, 1H), 8.08 (m, 1H), 8.34 (m, 2H), 8.65 (m, 1H)

(15-3) Quinoline-2-carboxylic acid 4-(2-hydroxycarbamoylvinyl)benzylamide

yield: 92% (pale brown solid)

^{1}H NMR (DMSO-d_6) δ 4.58 (d, 2H, J = 6.3 Hz), 6.43 (d, 1H, J = 15.9 Hz), 7.39 –7.46 (m, 3H), 7.53 (d, 2H, J = 8.1 Hz), 7.73 (m, 1H), 7.88 (m, 1H), 8.08–8.19 (m, 3H), 8.58 (m, 1H), 9.02 (br s, 1H), 9.51 (br t, 1H, J = 6.3 Hz), 10.72 (br s, 1H)

Example 16: In Vitro Cytotoxicity

Three human cancer cell lines (A-549, lung cancer; SK-BR-3, breast cancer; MKN-45, stomach cancer) were tested in MTT assay. These cell lines were grown in RPMI 1640 medium supplemented with penicillin–streptomycin (100 units/mL) and 10% heat-inactivated fetal bovine serum under standard culture condition (20% O_2 and 5% CO_2, 37°C). Single-cell suspensions were prepared by trypsinization and pipette disaggregation. The number of cells for each cell line plated in 96-well microtiter plates was determined from the growth curve obtained in MTT assay. Test compounds were diluted from stock solution in DMSO into fresh medium to a 10×concentration. Cells were inoculated into each well in 180 μL of medium and eight different concentrations of 20 μL of test compounds were added to each well. The plates were

then incubated for 4 days at 37℃, 5% CO_2. After 4 days of culture, 0.1 mg (20 μL of 5 mg/mL) of MTT was added to each well. The plates were then incubated at 37℃ for 4 hours. After the plates were centrifuged at 1,000 rpm for 10 minutes, the supernatant was aspirated. 150 μL of DMSO was added to each well to solubilize formazan crystals. The plates were read immediately at 550 nm on Elisa reader (Dynatech, MR 5000). The IC_{50} was defined as the concentration of compounds that produced a 50% reduction of surviving cells and calculated by quantal probit analysis of pharmacologic calculations with computer program.

Table 1. In vitro cytotoxicity of test compounds in the human cancer cell lines

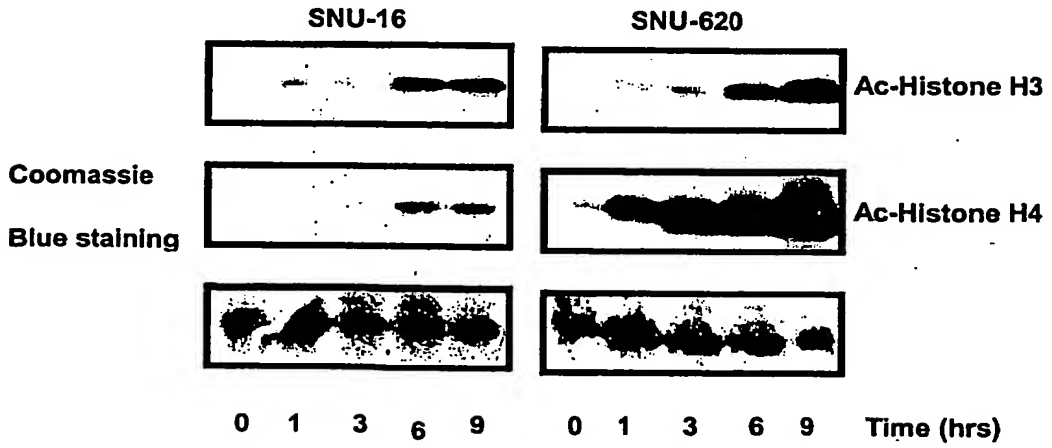
Compound	IC_{50} (μM)		
	A-549	SK-BR-3	MKN-45
Example 1	11.98	3.19	38.59
Example 2	1.65	0.27	2.94
Example 3	3.02	1.72	56.06
Example 4	2.23	0.87	3.64
Example 5	0.35	0.11	0.80
Example 6	0.48	0.16	0.83
Example 7	2.89	1.28	4.98
Example 8	2.61	1.12	3.34
Example 9	36.96	22.90	61.97
Example 10	11.08	4.57	8.34

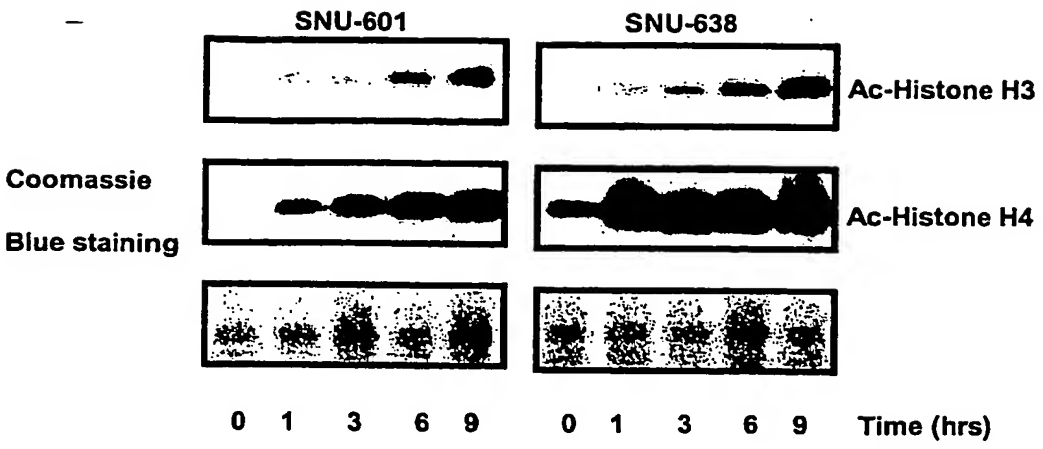
Example 17; In Vitro Inhibition of Histone Deacetylase

Four human gastric adenocarcinoma cells (SNU-16, 601, 620 and 638) were obtained from the Korean Cell Line Bank and grown in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum and gentamycin (10 μg/mL) under standard culture condition (20% O_2 and 5% CO_2, 37°C). Test compounds were dissolved in DMSO and used at a final concentration of 1 μM.

Cells (5×10^6) were cultured with and without a test compound (1 μM). Cells were pelleted and resuspended in 1 mL ice-cold lysis buffer (10 mM Tris-HCl, pH 6.5/50 mM sodium bisulfite/1% Triton X-100/10 mM $MgCl_2$/8.6% sucrose) before homogenization with two dounce strokes. Nuclei were centrifuged at 700 rpm for 5 minutes and washed 3 times with 1 mL of lysis buffer. The final wash was performed with 1 mL of Tris-EDTA solution (10 mM Tris-HCl, pH 7.4/13 mM EDTA). Nuclei were pelleted and resuspended in 100 μL of ice-cold water. Sulfuric acid was added to the samples to a final concentration of 0.2 M; samples were vortexed and incubated on ice for 1 hour. Samples were centrifuged at 13,000 rpm for 10 minutes at 4 °C, and the supernatant was precipitated with 1 mL of acetone overnight at –20 °C.

Figure 1. In vitro inhibition of histone deacetylase by Example 5



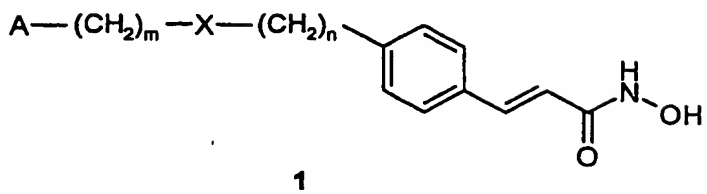


Precipitated protein was collected by centrifugation at 13,000 rpm for 10 minutes at 4 - °C, air dried, and resuspended in 50-100μL water. Proteins (20 μg protein) were denatured at 100°C in loading buffer for 5 minutes and electrophoresed in 15% polyacrylamide gels. After electrophoresis, samples were transferred onto nitrocellulose (0.2 μm) and probed with antibody to acetylated histone H3 or H4 (Upstate Biotechnology Inc.) as recommended by the manufacturer. Detection was performed using enhanced chemiluminescence system (Amersham). To verify equal protein loading, a parallel protein gel was run and stained with coomassie blue.

Claims

What is claimed is:

1. A compound represented by formula (1):



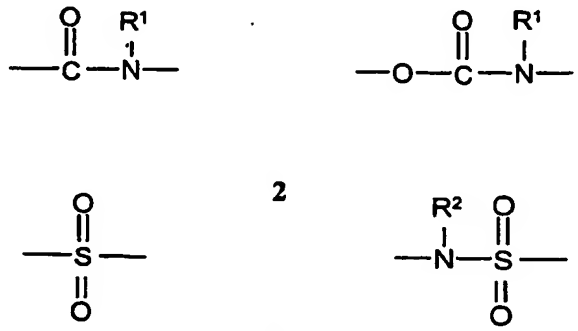
1

wherein A is an optionally substituted phenyl or aromatic heterocyclic group which has 1 to 4 substituents selected from the group consisiting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkoxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group, an aromatic heterocyclic group and a heterocyclic group, said heterocyclic group being optionally substituted with an alkyl group having 1 to 4 carbons, a benzyl group, or a pyridylmethyl group;

m is an integer of 0 to 4;

n is an integer of 1 to 4;

X is a moiety having a structure selected from those illustrated in formula (2)



2

R^1 and R^2 are independently H or an optionally substituted alkyl group having 1 to 4 carbons; or

a pharmaceutically acceptable salt thereof.

2. A compound of formula (1) according to claim 1 selected from the group consisting of

N-[4-(2-Hydroxycarbamoylvinyl)benzyl]-4-pyrrolidin-1-ylbenzamide

4-Dimethylamino-*N*-[4-(2-hydroxycarbamoylvinyl)benzyl]benzamide

3. A pharmaceutical composition comprising a compound of formula (1) according to claim 1 in combination with a pharmaceutically acceptable excipient or diluent.

4 . Use of a compound according to claim 1 for the preparation of a medicament having histone deacetylase (HDAC) inhibitory activity.

5. Use of a compound according to claim 4 as an inhibitor of cell proliferation.

6. Use of a compound according to claim 4 as an antitumor agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 03/00721-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 241/04, C07C 259/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN Karlsruhe: REGISTRY and CA Databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/22577 A2 (NOVARTIS AG) 21 March 2003 (21.03.03) *examples 78,159,160,162 and 176.*	1,3-6
A	*claims.*	2
A	WO 01/38322 A1 (METHYLGENE INC.) 31 May 2001 (31.05.01) *claims.*	1,2,3,4

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed

„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2003 (23.06.2003)	12 August 2003 (12.08.2003)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer SLABY S. Telephone No. 1/53424/348

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 03/00721-0

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1 and 3-6
Claim 2: The general formula of claim 1 does not comprise the compounds of claim 2.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 03/00721-0

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO A 138322		none	
WO A 222577		none	